
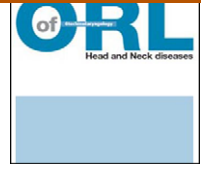




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## CLINICAL COMMENTARY

# Amyloid goiter: First manifestation of systemic amyloidosis

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### KEYWORDS

Amyloidosis;  
Goiter;  
Crohn's disease

**Summary** Amyloidosis is an abnormal extracellular deposit, which can occur in several tissues. The mechanism is not clearly defined. In systemic amyloidosis, all the organs can be infiltrated, but amyloid goiter as the initial manifestation of systemic amyloidosis is an exceedingly rare condition. We report a rare case of a patient who presented an amyloid goiter as the first manifestation of systemic amyloidosis. This patient had a known Crohn's disease. He developed a goiter without compressive complications. Histologic examination revealed a diffuse amyloid deposition surrounding thyroid follicles. The gland was enlarged with an eosinophilic and amorphous deposit. Confirmation of amyloid was made by the presence of congophilia and apple-green birefringence under polarized-light microscopy. An immunoreactivity was seen with AA protein. Amyloid goiter is a rare manifestation of amyloidosis. About 250 cases of amyloid goiter have been reported in the literature. The goiter enlarges rapidly and progressively, often becoming compressive like thyroid cancer. The prognosis depends on the treatment of the amyloidosis and the underlying chronic disease.

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## Introduction

Amyloid-associated (AA) or inflammatory amyloidosis is one of the main forms of systemic amyloidosis, along with immunoglobulin-associated and hereditary amyloidosis. In AA amyloidosis, the amyloid protein is AA protein, originating from serum amyloid-associated (SAA) protein, one of the main proteins involved in inflammatory reaction.

Consequently, almost any disease associated with chronic inflammation of whatever etiology is liable to amyloidosis complications [1].

Amyloid infiltration of the thyroid gland is common, but an aspect of secondary goiter with amyloid deposits is rare. Clinically, it is seldom considered, even in case of known amyloidosis [2,3]. Amyloid goiter has been exceptionally reported as the first manifestation of systemic amyloidosis [4].

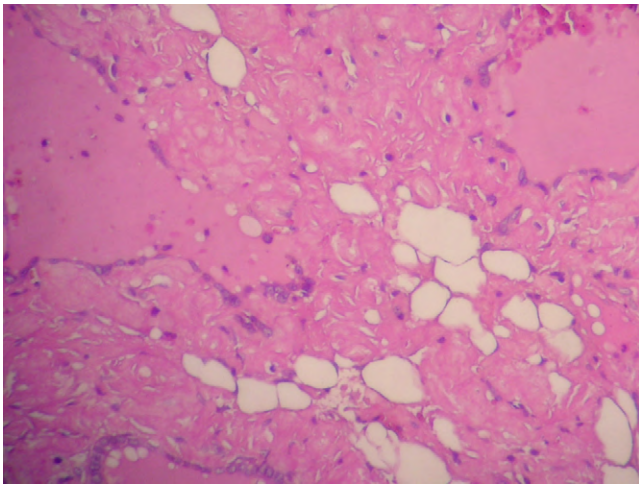
## Observation

A patient known to have Crohn's disease presented with goiter without signs of compression and with normal thyroid

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**Figure 1** Thyroid amyloidosis: interstitial tissue expanded by abundant amyloid deposit of mature adipose clusters between thyroid follicles (HE  $\times 400$ ).

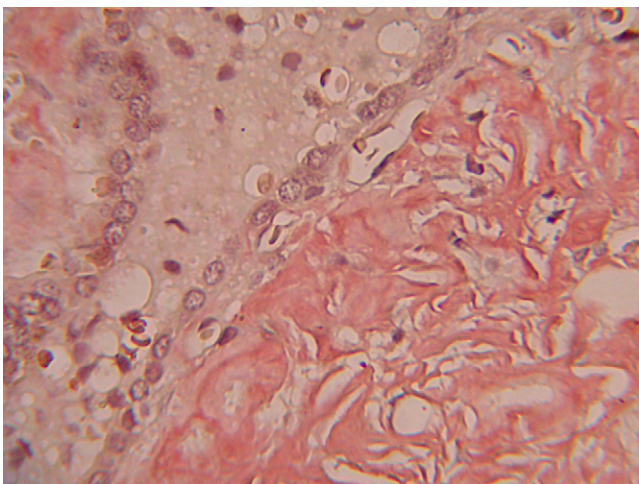
function. Cervical ultrasound found a right thyroid nodule. Lobo-isthmectomy was performed and the specimen was submitted to analysis.

Examination found a  $10 \times 6\text{-cm}^2$  thyroid lobe connected to a  $2 \times 1\text{-cm}^2$  isthmus. Sectioning disclosed a homogeneous brownish aspect without discernable nodule. A diagnosis of thyroiditis was initially considered, but was ruled out by the final result, which pointed rather to thyroid amyloidosis. The interstitial tissue was expanded by an acellular eosinophil deposit, interpreted as fibrosis on histology. A few mature adipocyte clusters were to be observed between the thyroid vessels (Fig. 1).

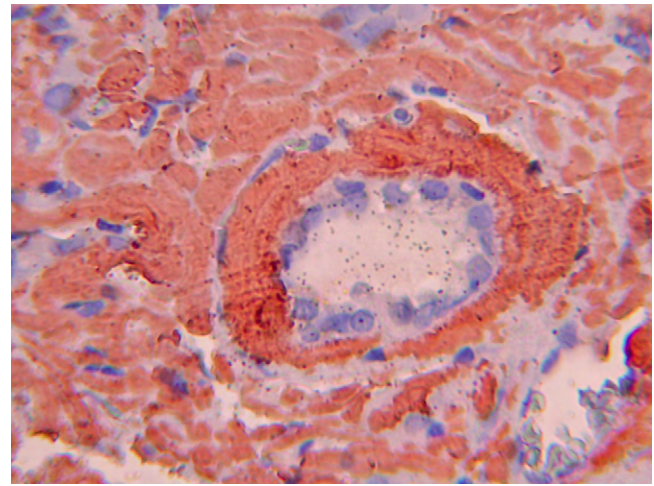
The deposit was marked brick-red on Congo red staining (Fig. 2), showing yellow-green double refraction under polarized light.

Immunohistochemistry classified the deposit as AA (Fig. 3).

This finding led to exploration for systemic amyloidosis, subsequently diagnosed on several biopsies.



**Figure 2** Congo red staining marks the deposit (Congo Red  $\times 400$ ).



**Figure 3** Immunohistochemical study on paraffin section: the amyloid deposit is of type AA (anti-AA antibody  $\times 400$ ).

## Discussion

AA amyloid protein, found in amyloid deposits, derives from the serum precursor, serum amyloid-associated protein (SAA). SAA protein is an apolipoprotein, involved in inflammation, during which its serum concentration increases 100 to 1000-fold under the influence basically of interleukin (IL)-6, IL-1 and tumor necrosis factor (TNF). Chronic serum SAA elevation is the basic determining factor in the onset of amyloidosis in chronic inflammatory disease [5]. This said, not all patients with chronic inflammatory disease and prolonged serum SAA elevation go on to develop amyloidosis. There must therefore be further genetic and environmental factors at work [1].

In developing countries, the etiology of secondary inflammatory amyloidosis is mainly infectious, whereas in Western countries chronic inflammatory rheumatism and other chronic inflammatory pathologies such as Crohn's disease, hemorrhagic rectocolitis or Whipple's disease are more often implicated [2]. Among tumors, renal cancer, hepatocellular carcinoma and lymphoma are most frequently implicated in AA amyloidosis. Castleman's disease is one of the most recently recognized causes and should be investigated in case of apparently idiopathic AA amyloidosis [1].

As chronic infectious disease becomes rarer and many chronic inflammatory diseases are better controlled, at least in the developed world, the epidemiology of this complication of inflammation is changing; while AA amyloidosis is becoming less frequent, its prognosis when it has taken hold remains poor.

Classically, amyloidosis tends to involve the heart, kidneys, lungs, gastro-intestinal tract or peripheral nervous system, but can also affect any other organ. Secondary systemic AA amyloidosis involves the thyroid in 80% of cases [6]. Infiltration by microscopic amyloid deposits is often discovered serendipitously, in thyroidectomy specimens or on autopsy. The deposits are asymptomatic, causing neither goiter nor dysthyroidism [2,7]; the quantity of amyloid deposits is rarely such as to impact thyroid volume. Only some 250 cases of amyloid goiter have indeed been reported worldwide [8].

Amyloid goiter may be diagnosed by cytopuncture [3,4], although there is a problem of differential diagnosis with medullary carcinoma, where amyloid deposit is also found in 50% to 80% of cases. Cytopuncture does, however, exclude other thyroid cancers, notably anaplastic cancer and lymphoma [6]. Anatomopathology enables positive diagnosis in case of amyloid deposit detected in the form of an amorphous substance showing yellow-green double refraction under polarized light on Congo red staining. As in the present observation, an aspect of adipose tissue interposed between the thyroid vessels is highly characteristic.

Amyloidosis typing is based on immunohistochemistry, as in the present case.

Eradicating infectious diseases such as tuberculosis or leprosy is of preventive value with regard to AA amyloidosis. It is certainly too soon to speak of the eradication of chronic inflammatory disease, but more powerful anti-inflammatory agents have reduced the incidence of associated amyloidosis over recent years. Regular monitoring of serum SAA could help in controlling inflammation and preventing amyloidosis [9].

Once amyloidosis has taken hold, etiological management of the underlying pathology remains mandatory.

Reducing the availability of amyloid protein precursor so as to halt deposit progression is at present the most logical treatment strategy in all forms of amyloidosis. In the case of AA amyloidosis, evolution seems directly bound to the control of inflammation and of serum SAA levels [10].

## Conclusion

AA amyloidosis is a serious complication of chronic inflammation. Incidence is falling as certain chronic infections become rarer and earlier and more powerful treatment of chronic inflammatory disease spreads. An aspect of amyloid goiter as the first manifestation of systemic amyloidosis is

exceptional, and rarely considered even in case of known amyloidosis.

Positive diagnosis of AA amyloidosis requires combined clinical and histologic data, and immunohistochemistry in particular, for differentiation with respect to other varieties. Once the disease established, prognosis remains poor.

Progress in treatment is needed, and notably the development of drugs targeting the early stages of amylogenesis.

## Conflict of interest

None.

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